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ON THE  
FORMATION OF URIC ACID IN ANIMALS;  
ITS RELATION TO  
GOUT AND GRAVEL.

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DR. P. W. LATHAM.

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TOGETHER WITH

AN EXPLANATION OF THE THERAPEUTIC EFFECTS  
OF SOME OF THE REMEDIES USED IN THE  
TREATMENT OF THOSE DISORDERS.

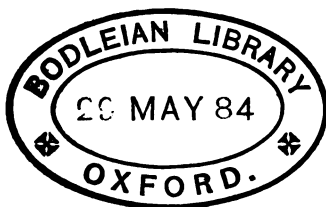
BY

P. W. LATHAM, M.A., M.D.

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PHYSICIAN TO ADDENBROOKE'S HOSPITAL, AND FORMERLY ASSISTANT  
PHYSICIAN TO THE WESTMINSTER HOSPITAL.

CAMBRIDGE:  
DEIGHTON, BELL AND CO.  
LONDON: GEORGE BELL AND SONS.  
1884.

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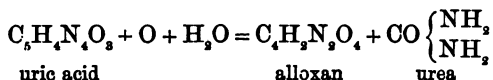
READ BEFORE THE CAMBRIDGE MEDICAL SOCIETY,

MARCH 7, 1884.

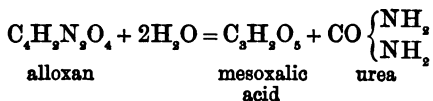
THE generally received notion with regard to the production of uric acid is that it is due to an incomplete oxidation of the nitrogenous principles in the animal system<sup>1</sup>, in other words, to a less perfect oxidation of the tissues than occurs when urea is formed. This view I believe to be only partially true; and I shall endeavour to shew in the first place that the formation of uric acid is in the human subject to a large extent due to defective assimilation or metabolism, and secondly that it is a "condensation product" much in the same way that cyanuric acid  $C_3N_3H_3O_3$  and biuret  $C_2H_5N_3O_2$  are condensation products of urea, or that cyanuric acid and in some degree allophanic ether  $CO \begin{Bmatrix} NH_2 \\ NH.CO.O C_2H_5 \end{Bmatrix}$  are condensation products of cyanic acid.

<sup>1</sup> Watts, *Dict. of Chem.* Vol. v. p. 955.

The main ground for the hypothesis that uric acid is due to defective oxidation is that by means of oxidising agents it can be split up into urea and other substances. For instance oxidised by nitric acid it is converted into alloxan and urea<sup>1</sup>,



and alloxan heated with baryta water is converted into mesoxalic acid and urea,



Or, if uric acid is oxidised by lead dioxide it is converted into allantoin, oxalic acid and urea<sup>2</sup>,



The view that the acid is due to defective oxidation has some support also from the fact, that in certain reptiles, as the Ophidians and Saurians, whose respiration is languid and whose temperature is low, the effete nitrogen of the system is eliminated in the

<sup>1</sup> Fownes' *Organic Chem.* 12th Ed. p. 402.

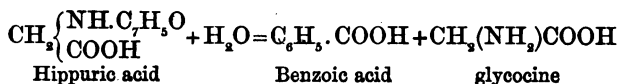
<sup>2</sup> *Ibid*, p. 412.

form of uric acid. But that this is not the true explanation or anywhere approaching to it is shewn by another fact that in birds whose temperature is higher than that of mammals and whose respiration is rapid, the urinary secretion contains very little urea and consists largely of uric acid, amounting in some cases to as much as 90 per cent. of the secretion. Further, in nearly all the invertebrata, whose temperature is high, the urinary secretion consists of uric acid or ammonium urate and contains no urea.

The diet has by some been thought to influence the secretion of uric acid; but in the urine of the carnivorous lion and tiger there is little uric acid and abundance of urea. In the carnivorous python and boa there is no urea but abundance of uric acid, and this is the case too in graminivorous birds, whilst in the herbivorous mammal the urine is rich in urea and in the adult contains no uric acid, though in the young of this class it is found in notable quantities. The diet then which in one class of animals produces uric acid, in another class produces urea, and *vice versa*; it by no means follows however that the amount of uric acid formed or excreted by the *same* animal should not be greatly

influenced by the diet; there is in fact no doubt that it is so influenced.

But whilst the urine of adult herbivorous mammals contains no uric acid this substance is replaced by hippuric acid,  $C_9H_9NO_3$ , varying in quantity both according to the food of the animal and according to the amount of work or exercise it has taken. Hippuric acid is also found though in much smaller quantity under normal circumstances in human urine. Now hippuric acid may be decomposed by boiling it with strong hydrochloric acid into benzoic acid and glycocine<sup>1</sup>



This action may be reversed and by heating benzoic acid and glycocine in a sealed tube to  $160^\circ\text{C}$ . hippuric acid is formed<sup>2</sup>. It may also be formed by injecting benzoic acid and glycocine, or bile into the blood of a living animal.

According to Kühne and Hallwachs<sup>1</sup> benzoic acid injected alone into the jugular vein, is not con-

<sup>1</sup> *Watts, Dict. of Chem.* Vol. III. 1865, p. 158.

<sup>2</sup> *Ibid.* p. 156.

verted into hippuric acid, but it is if injected into the portal vein. Meissner and Shepard<sup>2</sup> however state that after injecting benzoic acid into the jugular vein of a rabbit, at first benzoic acid alone appeared in the urine, then more and more hippuric acid, and lastly hippuric acid alone. These experimenters maintain that hippuric acid is formed in the kidneys alone, but benzoic acid appearing first alone in the urine in the above experiment would hardly bear out that view, and Salomon<sup>3</sup> after introducing benzoic acid into the stomach of a nephrotomized rabbit obtained a decided amount of hippuric acid from the muscles, liver, and blood. Again, when benzoic acid is injected into the portal vein of some animals at least, it appears as hippuric acid in the hepatic vein<sup>4</sup>. Hippuric acid also appears in the urine when benzoic acid is swallowed or introduced into the alimentary canal. Further, when oxygenized blood containing benzoic acid and glycocine is driven through the vessels of the living or recent kidney, it is found after its transit to contain hippu-

<sup>1</sup> *Jahresb.* 1859, S. 638.

<sup>2</sup> Meissner und Shepard, *Untersuchungen über das Entstehen der Hippursäure*. Hannover, 1866.

<sup>3</sup> W. Salomon, *Zeitschr. f. phys. Chemie*, S. 365, 1879.

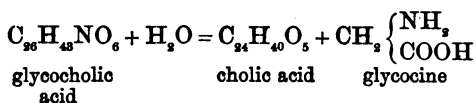
<sup>4</sup> Foster's *Physiology*, 4th Ed. 1883, p. 441.

ric acid<sup>1</sup>. Hippuric acid is also said to be formed when benzoic acid alone in *oxygenized* blood is driven through the living or recent kidney, but more hippuric acid is formed when glycocine is added<sup>2</sup>. It matters little for my present purpose, however, to discuss exactly where hippuric acid is formed; it is sufficient for me to point out three undoubted facts; first that if benzoic acid *and* glycocine are both introduced into the blood hippuric acid appears in the urine, secondly that if benzoic acid is swallowed or introduced into the alimentary canal of an animal, whether herbivorous or not, it appears in the urine as hippuric acid, having combined somewhere in its course with glycocine—and thirdly that the conjugation of benzoic acid and glycocine which takes place in the body at the normal temperature 37°—38° C. requires for its production out of the body a sealed tube and a temperature of 160° C. This last point especially we shall find has an important bearing on our discussion—and I particularly call attention to it.

<sup>1</sup> A. Hoffmann, *Chem. Centr.* 1877, S. 409.

<sup>2</sup> Hermann, *Handbuch d. Phys.* 1883, Bd. v. S. 307, and Bunge and Schmiedeberg, *Arch. f. exp. Pathol u. Pharm.* Bd. vi. 1876. S. 233.

Now we know that glycocholic acid is one of the acids contained in the biliary secretion, and that by boiling it with alkalis it is resolved into glycocine and cholic acid<sup>1</sup>.



We further know that this same decomposition takes place naturally in the alimentary canal, and that after the acid has served its purpose in digestion the glycocine is absorbed, passes transformed into the blood to be converted into urea, and as such subsequently eliminated by the kidneys<sup>2</sup>.

The fact that glycocine as well as other amidobodies such as leucine  $\text{C}_6\text{H}_{10} \left\{ \begin{array}{l} \text{NH}_2 \\ \text{COOH} \end{array} \right.$  and tyrosine  $\text{C}_9\text{H}_9 \left\{ \begin{array}{l} \text{OH} \\ \text{C}_3\text{H}_3(\text{NH}_2)\text{COOH} \end{array} \right.$  when introduced into the alimentary canal are absorbed in the normal state of things into the system and reappear in the urine as urea, has an important bearing on our subject. In an abnormal state, these substances appear in the urine, and in disease of the liver

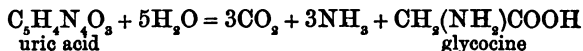
<sup>1</sup> Fownes' *Organic Chem.* 1877, p. 622.

<sup>2</sup> Foster's *Physiology*, 4th Ed. 1884, pp. 249 and 439.

such as acute atrophy, urea disappears almost or entirely from the secretion, its place being taken by leucine, tyrosine, &c.<sup>1</sup> From what I have said, too, it is clear that the conversion of glycocine into urea, wherever the glycocine may be formed, may be prevented by the administration of benzoic acid, the resulting compound passing into the urine as hippuric acid, from which substance glycocine but not urea can be obtained.

But it is not correct to say that the whole of the glycocine formed in the system is transformed into urea or passes off as hippuric acid. A portion of it is eliminated as a constituent of uric acid, and this is a point to which attention generally has not been sufficiently directed. This fact is the basis of my present remarks and the keystone of my theory.

If uric acid is heated in a sealed tube to 160°—170° C. with a cold saturated solution of hydriodic acid, it is decomposed with the formation of ammonium iodide, carbonic acid and glycocine<sup>2</sup>.

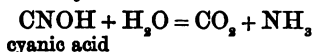


We see then that just as hippuric acid may be

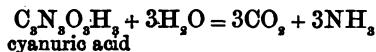
<sup>1</sup> Frerichs, *Klinik der Leberkrankheiten*, 1858, S. 206.

<sup>2</sup> Strecker, *Zeitschr. f. Chem.* [2] iv. 215.

said to be built up from residues of glycocine and benzoic acid so uric acid is built up from residues of glycocine and some substance which splits up into equal molecules of  $\text{CO}_2$  and  $\text{NH}_3$ . Cyanic acid will split up in this way

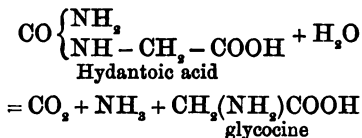


decomposing in this fashion even when simply mixed with water—so also will its very stable polymeride cyanuric acid



a substance which has some properties in common with uric acid, viz. that it is soluble in solution of sodium phosphate, it is soluble also in strong sulphuric acid and in solutions of the alkalis, and can be precipitated from the one by water and from the other by acids.

There is further another body which when heated with hydriodic acid is converted like uric acid into glycocine, ammonia and carbonic acid—viz. hydantoic acid<sup>1</sup>.

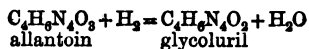


<sup>1</sup> Fownes' *Organic Chem.* p. 410.

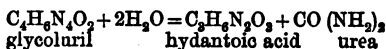
Hydantoic acid can be obtained from uric acid, and there are three other derivatives from uric acid, viz., allantoin, glycoluril and hydantoin, from which hydantoic acid and therefore glycocine can be obtained<sup>1</sup>. It follows then that as glycocine can be obtained not only directly from uric acid but also from these various derivatives it is an essential factor or constituent of that acid.

Now hydantoic acid can be formed synthetically, and here we have the first step towards the synthesis of uric acid. By heating urea and glycocine to a

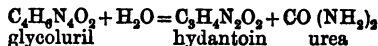
<sup>1</sup> The formation of allantoin from uric acid has already been given. By the action of sodium amalgam on allantoin, glycoluril is produced



By the action of baryta water this is converted into hydantoic acid and urea



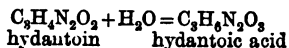
or boiled with acids it is converted into hydantoin and urea



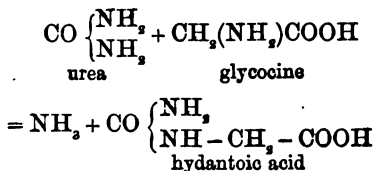
Hydantoin may be obtained also directly from allantoin by means of hydriodic acid



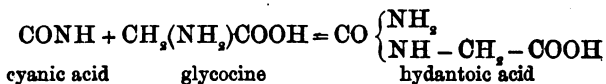
and hydantoin boiled with baryta water gives hydantoic acid



temperature of 120°—125° C. they combine and form hydantoic acid<sup>1</sup>



And this acid can also be obtained by heating glycocine sulphate with potassium cyanate<sup>2</sup>



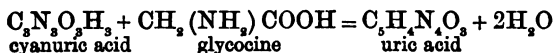
Regarding then the decomposition of uric acid with hydriodic acid, we see from it that if glycocine could be combined with three molecules of cyanic acid we should have a body which would undergo a similar decomposition to uric acid, or if the glycocine were combined with three molecules of urea, and three molecules of  $\text{NH}_3$  evolved, a similar body would be produced.

Acting upon these data I have made a number of experiments, two of which, though unsuccessful, are worth mentioning. Cyanuric acid and glycocine

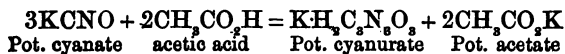
<sup>1</sup> Heintz, *Jahresb. für Chem.* 1835, S. 360.

<sup>2</sup> Wislicenus, *Liebig's Annalen*, cXLV. S. 103.

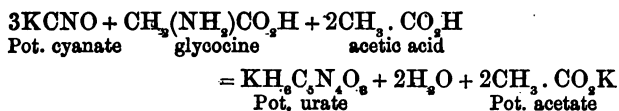
were put into a sealed tube and heated to 200°—220° C. They were also heated together in strong sulphuric acid. The formula is theoretically correct,



but the results so far have been negative. The other experiment was based on the fact that if acetic acid be added to potassium cyanate, cyanurate is formed according to the following equation<sup>1</sup>



Potassium cyanate and glycocine were dissolved together in water and acetic acid added, with a view to the following decomposition:



but cyanuric acid was the result, uncombined with the glycocine.

Whilst these experiments were being made a paper appeared in the *Berichte* for Nov. 1882, page 2678, on the synthesis of uric acid, by Horbaczewski.

<sup>1</sup> Miller's *Organic Chemistry*, Part III. 1880, p. 122.

He states that by heating glycocine with ten times its weight of urea to 200°—230° C. he obtained a cloudy and thick fluid. This on cooling was dissolved in weak potash solution and supersaturated with ammonium chloride and precipitated with an ammoniacal solution of silver and magnesia. This precipitate containing the uric acid was washed with water containing ammonia and decomposed with potassium sulphide. The filtrate freed from the precipitate was supersaturated with hydrochloric acid and evaporated down. On cooling the impure uric acid separated, which was again dissolved in a weak solution of potash and submitted twice to the same process as above. Lastly the product was washed with alcohol and dried. It was next treated with bisulphide of carbon to dissolve the sulphur, and then treated with ether.

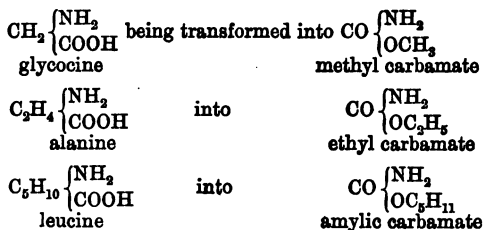
I have tried the experiment, carefully following the directions as above, but have hitherto failed to obtain the wished-for substance. Nor have I yet seen anywhere that Horbaczewski's experiment has been verified. If it is verified, then I have no doubt that uric acid will also be obtained by experiments similar to my own, either from cyanic acid or from substances containing the molecule

$\text{CO} - \text{NH}_2$ , such as the alcoholic carbamates or urethanes

$\text{CO} \left\{ \begin{array}{l} \text{NH}_2 \\ \text{OR} \end{array} \right.$ , where R stands for any alcoholic radicle<sup>1</sup>.

But though these experiments have so far been unsuccessful in my hands, I do not regret the time which has been bestowed upon them. In considering the changes which have taken place, certain points have suggested themselves which I think

<sup>1</sup> I refer here to the alcoholic carbamates because two years ago (see *Lancet*, Vol. i. 1882, p. 611) I suggested that glycocine, alanine, leucine, &c., in the process of conversion in the animal body into urea, first underwent a molecular transformation into their corresponding alcoholic carbamates,

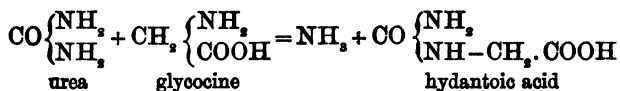


and that these carbamates then meeting with  $\text{NH}_3$  were transformed into urea and the corresponding alcohol—to effect which out of the body requires a temperature of  $180^\circ \text{C}$ . in a sealed tube—I believe more strongly than before that these carbamates are the immediate antecedents of urea, but not that they are simple molecular transformations of the amido-bodies. I hope before long to be able to point out however in what way the latter are decomposed, so as to lead to the formation of the carbamates.

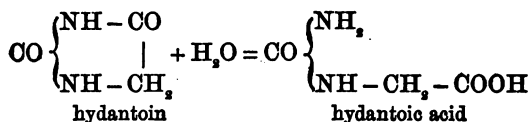
of great importance, and to which I now wish to direct attention.

The first suggestion I have to make is that in endeavouring to arrive at the synthesis of uric acid, the process must be divided into two, if not three, stages.

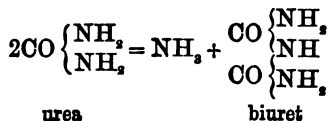
I have already alluded to the fact that by heating glycocine with urea or cyanic acid, hydantoic acid is formed



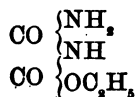
and hydantoic acid is also obtained by boiling hydantoin with baryta water



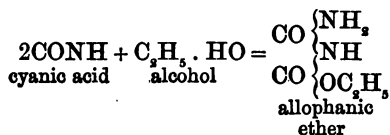
By heating urea alone to a temperature somewhat higher, viz. to 150°—160° C., condensation takes place, and it is converted into biuret  $\text{C}_2\text{O}_2\text{N}_2\text{H}_2$ .



This substance is the amide of allophanic ether,

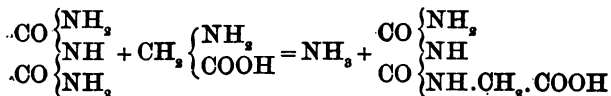


that is, the molecule  $\text{NH}_2$  can be replaced by  $\text{OC}_2\text{H}_5$ , or generally by  $\text{OR}$ , where  $\text{R}$  stands for any alcoholic radicle. Now allophanic ether is obtained by passing cyanic acid vapour into absolute alcohol,

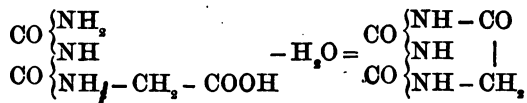


condensation of two molecules of cyanic acid taking place.

If now glycocine were combined with either of these bodies,  $\text{NH} \cdot \text{CH}_2\text{COOH}$  as in hydantoic acid, replacing either  $\text{NH}_2$  in the biuret, or  $\text{OC}_2\text{H}_5$  in the allophanic ether, we should have

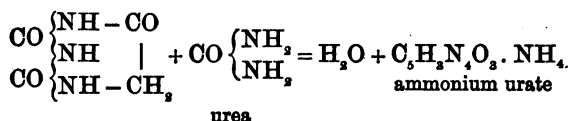


a body containing one more molecule of  $\text{CONH}$  than hydantoic acid, and which dehydrated



forms a body having a similar relationship to hy-dantoin; that is contains one more molecule of CONH, and is isomeric with uramil  $C_4H_8(NH_2)N_2O_3$ , though differing from the latter in constitution, having the molecules  $NH \cdot CH_2$  instead of  $NH_2 \cdot CH$ . By combining uramil with cyanate of potash, pseudo-uric acid, as we know, is formed<sup>1</sup>.

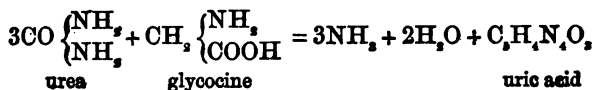
I venture to think therefore that in the synthesis of uric acid this body, intermediate to it and hy-dantoin, must first be obtained, and that the next step would be the combination of this substance with urea or with ammonium cyanate. The re-sulting compound would be ammonium urate



from which, on the addition of an acid, uric acid would be obtained.

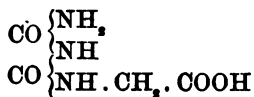
<sup>1</sup> Treating allophanic ether with caustic baryta (Fownes' *Org. Chem.* p. 395) it yields the barium salt of allophanic acid— $C_2H_4N_2O_3$ , but the acid itself cannot be obtained in a free state, as when separated from the barium salt by a mineral acid it is immediately resolved into urea and carbon dioxide. Possibly by treating this barium salt with glycocine sulphate a successful result might be obtained.

If Horbaczewski's experiment is verified, the following equation would represent the changes



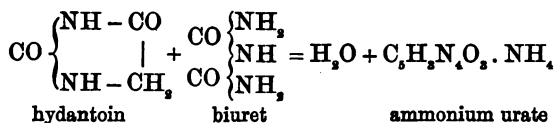
After the temperature is raised above 120° C. ammonia is given off during the entire process. At 120°—130° C. hydantoic acid would certainly be formed. At 150°—160° C. biuret is formed; and the interesting question arises, Will the hydantoic acid combine at that temperature with one more molecule of CONH<sub>2</sub>, or will the molecule NH<sub>2</sub>.CH<sub>2</sub>.COOH replace one molecule of NH<sub>2</sub> in the biuret?

At the temperature now reached, the remaining portion of the urea has been all transformed into condensation products, and it appears to me, that the next step necessary is to dehydrate the body



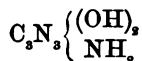
and then heat with a fresh portion of urea. The process, if true, could however be explained as follows. The hydantoic acid, if dehydrated between 130° and 160° C. and converted into hydantoin, would

combine with the biuret formed at that temperature, and we should have

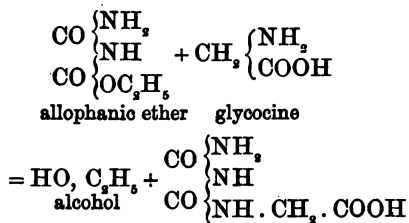


In one experiment, to test Horbaczewski's, I took 45 grains of glycocine and 450 of urea; these were heated rapidly to a temperature of 230° C. exactly, at which point the mass becomes almost solid. This was treated with (*a*) cold water, (*β*) boiling water, after which 132 grains of insoluble residue (*γ*) remained, but which was quite soluble in potash. These three portions were all tested in various ways for uric acid with negative results. On evaporating (*a*) a very small amount of needle-shaped crystals was obtained; (*β*) on cooling deposited substances of different solubility, the more soluble portion presenting very much the appearance of lithates in urine, the more insoluble appearing as nodular crystals, which, when placed under the microscope, had very much the appearance of uric acid, rhombic tables with obtuse angles rounded off, and some diamond- or lozenge-shaped, but on boiling with animal charcoal and filtering, the crystals presented

the ordinary appearance of cyanuric acid and answered to the tests for that substance; ( $\gamma$ ) was apparently nothing more than ammelide



In another experiment allophanic ether was heated with glycocine to 200° C. in an open tube, ethylic alcohol was given off and a substance remained, which appeared to possess distinctive characters. It is soluble in water, gives no precipitate with lead acetate, a distinct one with lead subacetate, and a copious one with mercuric nitrate: whether this is the substance which would result from the following formula remains for further investigation.



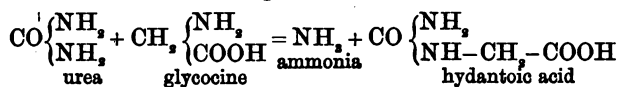
I only regret that the exigencies of professional life will not allow me the necessary leisure to follow up these interesting investigations and speculations, and that it is only at intervals that I can make any

experiments. I shall be glad however if the suggestions I have here put forth are considered by those having a more intimate acquaintance with chemistry and chemical manipulation than I possess, and, if it is thought worth while, carry them into practice.

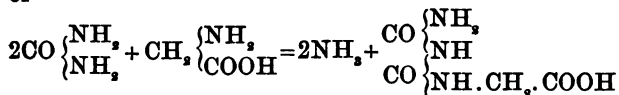
Let me now apply this view of the formation of uric acid to explain its production in the animal economy—and the explanation really becomes a very simple one.

In the human subject glycocine conjugated with cholic acid is poured out as glycocholic acid, a constituent of the bile, into the intestine. After the bile has served its purpose in digestion, the glycocine as well as taurine are returned into the blood. These together with the other amido-bodies, leucin, and possibly tyrosin, the products of the digestion of albuminous food, reappear in the urine as urea; that is, the urine does not contain them, but its urea is proportionately increased. Now these amido-bodies, glycocine, leucine, &c., are probably carried by the portal vein straight to the liver, and from certain facts which I need not here detail we are led to the view that among the numerous metabolic

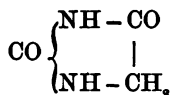
events which occur in the hepatic cells, the formation of urea from these bodies may be ranked as one. Suppose from some cause this metabolism of glycocine is interrupted (and I need only refer here to the interrupted metabolism of starch or glucose in diabetes as an illustration of what I mean), whilst taurine, leucine, &c., still undergo the normal changes into urea, we should then have in the gland the two substances, glycocine and urea, (or the immediate antecedent of urea) the conjugation of which by the gland (just as in the case of hippuric acid being formed from the conjugation of glycocine and benzoic acid) would produce either hydantoic acid, or the acid I have above referred to, containing two molecules of CONH,



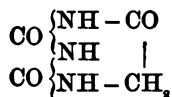
or



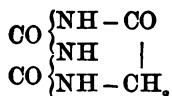
these dehydrated would be converted respectively into hydantoin



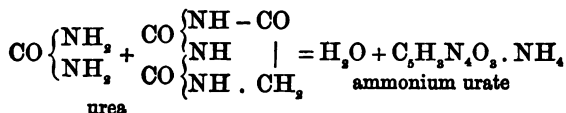
or into the substance



Hydantoic acid, hydantoin, biuret and glycocine are all easily soluble in water, and we may assume that this compound

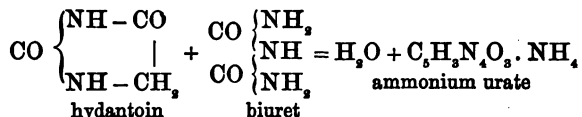


is soluble in water, or at all events that, like its isomeride uramil, it is soluble in an alkaline fluid like the blood. In this condition then it passes into the circulation, and arriving at the kidneys, is there conjugated with urea (taking again the conjugation of glycocine and benzoic acid as illustrating the power of the kidney in this respect), and is excreted as ammonium urate,



If hydantoin were formed in the liver then on

arriving at the kidneys it must be conjugated with biuret, to form ammonium urate.



This latter combination however I regard as less likely to take place in the system than the former one.

This view I think meets all the difficulties which have been raised with regard to previous theories as to the formation of uric acid; difficulties which have been very clearly set forth by Dr Garrod in his recent Lumleian lectures. Nor is it difficult to understand that if, as I have endeavoured to prove, the final conjugation of two soluble bodies takes place in the kidney forming the very slightly soluble ammonium urate 1—2400, a portion may not be excreted but remain in the blood, overflow as it were, and so pass on into the circulation; a result which certainly happens when the ureters are ligatured. The ammonium salt would then meeting with the soda in the blood be converted into sodium urate, the form in which it is deposited about gouty joints.

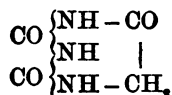
This view explains too why it is that the blood

of birds contains very little uric acid, though a very large daily secretion of this substance can take place amounting to as much as  $\frac{1}{150}$  of the bird's weight, or what would require twenty times the bird's weight of water for its solution.

The appearance then of uric acid in the secretion of one animal and of urea in another is the result primarily of the non transformation or metabolism of glycocine into urea—whether that glycocine be derived from the bile poured out into the duodenum or formed elsewhere in the body. That it is from the bile is made somewhat probable from the fact that in the carnivora whose urine contains little or no uric acid the bile contains no glycocholic but only taurocholic acid, therefore no glycocine.

I now come to the question of the abnormal formation of uric acid in the human system. Just as in diabetes the essential fault lies in the inability of the system, either in the liver, or it may be elsewhere, to effect the metabolism of glucose which then passes into the circulation and is discharged by the kidneys, so in gout or gravel the imperfect metabolism of glycocine is the primary and essential defect. Unchanged it passes from the alimentary canal or elsewhere, into the liver, there under the action of the

gland it is conjugated with urea resulting from the metabolism of the other amido-bodies leucine &c. and is converted into hydantoin or into the body



then passes on to the kidneys to be combined there with another molecule of urea forming ammonium urate, a portion of which overflows into the circulation and is converted into sodium urate. It is not difficult to understand that in persons who are addicted to the pleasures of the table, who are fond of port and who take little exercise the liver should become "sluggish" and its functions should be imperfectly performed—the result being the non-metabolism of the glycocine. But it is not every toper and gourmand who developes gout, nor is every gouty man necessarily a toper or a gourmand. We must look then somewhat further for an explanation, and we are led by various considerations to look upon some change in the nervous system as the most important factor in the etiology of the disorder. This change being localised in the medulla oblongata, or the spinal cord or both—and being either hereditary or acquired. And here we have an explanation of that

"hereditary tendency" which occupies such a prominent part in connection with the disease—and here also the reason why some people have uric acid gravel or calculus unaccompanied by gout.

If a portion of the medulla oblongata involving some of the roots of the vagus be a weak point, it is not difficult to understand that the function of the liver may be interfered with and that slight errors or excesses in diet would lead to very imperfect metabolism, and so to the formation of uric acid in the manner I have described. On the other hand if by free living the function of the liver were overtaxed so as to lead to the formation of uric acid in the blood, this circulating as a poison in the blood would act more particularly upon any weak spot in the nervous system and if that portion was in the neighbourhood of the roots of the vagus there might be developed hepatic derangement, gastric uneasiness, asthma or cardiac irregularities. And moreover if that alone were the weak spot in the nervous system the joints would probably be unaffected and renal or vesical calculi might be the only other accompaniment of the disorder. This hypothesis of a weak spot about the nucleus of the vagus will also explain the increased secretion of uric acid which sometimes

accompanies or alternates with diabetes, as well as the occurrence of megrim in connexion with gout.

If however in addition to some change in the medulla oblongata, portions of the spinal cord which control the nutrition of the joints are affected (and here I would refer to the rapid changes which take place in the joints sometimes in locomotor ataxy as an illustration of what I mean), then it is not difficult to understand that the uric acid acting upon these portions of the spinal cord will cause nutritive changes or inflammation in the joints in connection with that portion of the cord, and that as the blood conveys sodium urate to these inflamed joints, this substance should be deposited along with the nutritive material from the blood in the metabolism which take place in the tissues around the affected joint.

The facts that mental fatigue, worries or excitement will often induce an attack in individuals predisposed to gout, and that muscular fatigue especially after walking will do the same, give support to the view which I have here advanced.

In the former cases the function of the vagus is more or less inhibited, in the latter case you have spinal exhaustion from the fatigue. Lastly if the medulla oblongata were sound but the spinal cord

alone affected in the manner I have suggested, what symptoms might we expect? That the digestive functions and those of the liver would be properly performed and no uric acid formed; nutritive changes however would take place in the joints, but as the blood contains no abnormal amount of uric acid these changes would differ from those developed by gout. Should we not in fact have osteitis deformans or so-called rheumatoid arthritis?

The reason why gout so generally does not appear until after middle life is intelligible from the arguments here advanced. So long as the kidneys are sound and can throw off the uric acid as it is formed in them there is little overflow of the acid into the blood, but if the organ has been overtaxed, and has become weakened or diseased then as the blood passes through the kidneys the acid is formed but not eliminated. In this way too the occurrence of gout and an abnormal amount of uric acid which even in younger subjects is found in the blood in cases of albuminuria becomes intelligible.

The association of gout with chronic lead poisoning is easily explained by this theory. Just as in some individuals the presence of lead in the system induces those changes in the nervous tissues which

develope epilepsy, so in these cases the lead acts more particularly on those portions of the spinal cord which are concerned in gout.

One more suggestion. If the medulla oblongata and the spinal cord were affected in a somewhat modified way so that a different poison circulated through the system, would this not be sufficient to explain the phenomena of rheumatism? The poison in this case is supposed to be lactic acid which may be derived in the system from alanine  $C_3H_7(NH_2)COOH$  the next higher in the series of amido-bodies to glycocine. The curative action of salicylic acid in rheumatism may in some degree, I think, be due to its combining with this antecedent of lactic acid and so putting a stop to its formation. There are other antecedents of lactic acid however with which salicylic acid may combine but I will not at present push my hypotheses further. I merely mention these points in order to suggest that a careful microscopical examination of the medulla and spinal cord in these three disorders may still help to throw considerable light on their pathology.

That the nervous system was in fault in gout has been maintained by Cullen and many of the most accurate observers of former days. I will only

refer to two of the most trustworthy of modern times. Sir James Paget<sup>1</sup> says, "disturbance in the nervous system in some form and part may be regarded as a factor in every case of gout. There are reasons enough for thinking that changes in the nervous centre determine the locality of each gouty process, while changes in the blood and tissues determine its method and effects; and that thus we may explain the symmetries of disease in gout—sometimes bilateral, sometimes antero-posterior—and thus its metastases. But these changes are a part of its pathology which is not yet clinical."

Dr Edward Liveing<sup>2</sup> writes, "There can be no question then, I think, as to the frequent connexion of megrim, whether in its blind, sick, or simply hemicranial forms, with a gouty diathesis, and its occasional replacement by fits of regular gout. Megrim, however, is far from being the only neurosis which is thus associated with gout; a similar connexion may be traced in the case of asthma, angina pectoris, gastralgic paroxysms, and certain forms of transient mental derangement. The consideration suggests an interesting inquiry as to the

<sup>1</sup> *Clinical Lectures and Essays*, 1879, p. 382.

<sup>2</sup> *On Megrim and Sick-headache*, 1873, pp. 404—5.

nature of the relationship between these various neuroses and regular gout. The view which is commonly entertained is that the excessive generation or retention of uric acid in the system, which is regarded as the fundamental fact in the pathology of gout, exerts a toxic influence upon the nervous centres, while the particular character of the disorder is determined by the territory involved. This limited operation of a cause so general in its nature is a real obstacle to this view; on the other hand, there is much in the history of gout—its hereditary character, limitation to particular ages and sexes, periodicity, explosive character, sudden translations and remarkable metamorphic relations with nervous disorders—which seems to stamp the malady as a pure neurosis; and even the fit itself, with its sudden nocturnal invasion, the late Dr Todd was accustomed to compare to one of epilepsy or of asthma. Moreover, although the presence of uric acid in the blood of gouty subjects is no longer inferential and admits of ready demonstration, the dependence of the remaining phenomena of gout upon this associated condition is, to say the least, far from proved; and it is further certain that uric acid is also present in excess under other pathological conditions which

have no connexion whatever with gout. On the whole, there is much to be said in support of the view that gout in its various forms is the manifestation of a disorder which has its primary seat in the nervous system itself; and there is no more difficulty in conceiving that inflammation and pain may be an effect of deranged innervation in the case of Arthritis, than in the analogous case of Herpes Zoster; or that an excess of uric acid should be generated or retained in the system under a similar influence, than that sugar should in the parallel case of the diabetes which follows a lesion in the floor of the fourth ventricle."

From what I have advanced in this paper the parallelism between gout and diabetes would seem to be very close. In the one case the poison in the system results from the imperfect metabolism of glycogen or glucose, in the other from the imperfect metabolism of glycocine, and in both cases the nervous system is affected respectively by those substances or their derivatives.

Two very important points in connexion with the view I have here brought forward remain still for consideration, and I will not pass them unnoticed. How are the prodromata of gout, the depression,



gout—and which may also be produced by errors in diet or even by the direct administration of oxalic acid. The effect of the oxalic acid on the nervous system may be such as to intensify the force concerned in the production of urea and so give rise not only to increased metabolism of the tissues and to the further formation of urea, but also to condensation of the molecule CONH taking place. In this way I would explain the results obtained by E. Alleyne Cook<sup>1</sup> in experimenting upon himself. After taking oxalic acid, or substances such as tomatoes and rhubarb which contain that acid, the excretion of urea and that of uric acid were both much increased.

That nerve force is unnecessary and that condensation of two or more molecules of CONH may take place independently of it, is clear from the action of acetic acid on potassium cyanate producing potassium cyanurate and from the combination of cyanic acid with alcohol producing allophanic ether. The behaviour however of urea when electrolysed is very remarkable. Professor Dewar has recently discovered that it is an electrolyte, and one result of the electrolysis is the formation of biuret. He has kindly fur-

<sup>1</sup> *British Med. Journal*, 1883, Vol. I. p. 246.

nished me with the details of the experiment, and given me permission to refer to it. They are as follow :

*Electrolysis of Urea.*

Pure urea heated to about 120° was used. Battery power = from 10 to 30 pint Groves, according to the resistance.

Ammonia and hydrogen are given off at the negative pole but no gas could be obtained from the positive.

When the current passed after a time, the temperature of the urea rose considerably, great care was taken never to allow it to rise above 150°. Heated within the range of 150° there was no appearance of decomposition.

The fusing point of the urea, as the electrolysis proceeds, appears to become lower, reaching in one experiment, after intermittent electrolysing for some six hours, as low as 98°.

The urea after electrolysis was dissolved in water and tested, when it was found to contain at the most but a mere trace of cyanuric acid along with a considerable quantity of biuret.

In one experiment instituted to prove that the

temperature did not rise high enough to decompose the urea by itself, a small flat bulb filled with urea was placed in the centre of the decomposing apparatus where it had every chance of being heated. On examination of the contents of the small bulb on the completion of the experiment no cyanuric acid was found and but the slightest trace of biuret.

*Composition of the Gases given off by Electrolysis.*

Samples were taken during the progress of the experiment. In the first two samples only ammonia and hydrogen were estimated, in the last the analysis is complete.

	After 1 hour.	After 2 hours.	After 3 hours.
Ammonia	74·2	64·3	34·6
Hydrogen	13·3	13·2	50·1
Nitrogen	—	—	15·2
			<u>99·9</u>

If there be any correspondence at all between nerve-force and the electrical current, this experiment possesses great significance.

I come now to the most important question, How will this theory help us in the treatment

of those disorders which are usually associated with the excessive formation of uric acid, viz. "gout" and "gravel"?

I will endeavour to support the theory I have advanced by considering what light this theory throws on the actions of those remedies which clinical experience has taught us are useful in the treatment of those disorders. From the evidence I have brought forward with regard to the constitution of uric acid, it follows that if glycocine when formed in the system were to undergo its proper metabolism into urea, or if it were otherwise eliminated from the system, uric acid could no longer be formed.

When horses are kept in the stable or only lightly worked their urine contains hippuric acid, but when they are put to hard work it contains benzoic acid<sup>1</sup>. The effect consequently of muscular exercise is either to prevent the formation of glycocine, or if formed to promote its metabolism into urea. Here then is an explanation why those with a tendency to gout who take little exercise develop the disease, but for the reasons I have given in a previous part, the exercise taken to prevent

<sup>1</sup> Watts' *Dict. of Chem.*, Vol. III. p. 156.

its development must be not so great as to produce fatigue. "In such cases you must trim," as Sir Thomas Watson<sup>1</sup> so happily puts it, "as well as you can, between opposite dangers; between the Scylla of excess, and the Charybdis of debility. . . . The young and the hearty can scarcely take too much: the old and the dilapidated, by one act of over-exertion, may incur the penalty of an attack. Although I can do little more than point out general principles for your guidance, I may remark, in reference to exercise, that it should never be *violent*, lest it excite a paroxysm by straining any part, or by causing great fatigue: that it should be *habitual*, daily—not used by fits and starts, and interrupted by long periods of indolence and inaction: and that it should be *active* muscular exercise, as distinguished from passive exercise or gestation. No mode of exercise is so good as that of walking; and with this may be agreeably and beneficially conjoined riding on horseback."

The diet should be simple and nutritious; jellies and food containing gelatine should be avoided, as this substance furnishes glycocine. Animal food itself will not produce uric acid in a healthy system,

<sup>1</sup> Watson's *Pract. of Physic*, 4th ed. Vol. II. p. 772.

as is shewn by its absence in the urine of the carnivora, but from all kinds of meat a certain amount of glycocine will be produced, and even if all the rest of the nitrogenous portion after being absorbed into the system were converted into urea, this would necessitate an increased elimination of urea, and consequently a greater tax on the powers of the kidneys. If these powers are weakened there will be, with an increased call upon the organs, less power to act, and not only would the urea but still more the uric acid accumulate in the blood. The striking benefit and increased urinary secretion which result in some forms of albuminuria from a skim-milk diet, that is, the simplest of all diets, very well illustrate what I mean here. The presence of urea in the blood may, by its action on the nerve-centres, determine an increased blood supply to the kidneys, and so, in a healthy state of things, an increased secretion, but if the secretory portion is damaged, or the nerve force controlling it defective, an increased flow of blood to the part, producing a congested condition of the organ would not expedite, it would rather hinder, the work of the secretory portion. The effect of stimulation of the chorda tympani

upon the secretion from the submaxillary gland, after a small quantity of atropin has been injected into the veins<sup>1</sup>, illustrates very well this condition. The simpler the diet then, the less tax there will be upon the kidneys, and the better they will do their work. Let the diet then be chiefly farinaceous, with just sufficient nitrogenous food to satisfy the wants of the system—and in acute attacks let that be in the form of milk, diluted even, if necessary.

By proper exercise and diet then the formation of glycocine may be lessened. If it is formed, how is it to be got rid of? First, by laxatives—not by violent purgatives however, which, by weakening the patient, would increase the power of the poison on the nervous system—and by such laxatives as will promote the discharge of bile from the intestines, after it has been secreted from the liver. In this way the biliary acids are eliminated from the intestines, the reabsorption of the glycocine, and the consequent formation from it of uric acid prevented. I will not discuss here whether calomel is a cholagogue, i.e. promotes the flow of bile from the liver, or not. It is sufficient for my purpose to point out that when the bile gets into the intestine calomel

<sup>1</sup> See Foster's *Physiology*, 4th Ed. p. 260.

will cause its evacuation. "The conclusion seems inevitable, that mercurial purgatives given to healthy persons cause the escape of large quantities of bile from the alimentary canal<sup>1</sup>." In some persons calomel has a depressing effect, and when the kidneys are affected is injurious in its action, but in the earlier attacks of gout I have often seen marked relief follow its administration. Where calomel is inadmissible rhubarb is often of service. When the object is simply to unload the bowels in a debilitated subject it is the best purgative. It is said to act chiefly by increasing the peristaltic action of the bowels throughout their entire extent, but especially that of the duodenum. According, to Rutherford, it is a cholagogue. Sir Henry Hallford recommended it as a prophylactic remedy against gout, a few grains of rhubarb with double the quantity of magnesia every day: or some light bitter infusion with tincture of rhubarb and about fifteen grains of bicarbonate of potash.

The saline cathartics probably act only by causing serous evacuations and in that way carry off from the blood some of the poison contained in it. They

<sup>1</sup> H. C. Wood, junr. *Treatise on Therapeutics*, 2nd ed. 1877, p. 435.

may also act beneficially perhaps by relieving a congested liver.

Secondly, we may administer such remedies as will combine with glycocine and so prevent the formation of uric acid. It is in this way that benzoic acid acts; passing out in the urine as hippuric acid—and gouty patients undoubtedly derive benefit from its use. Dr Golding Bird prescribed it in conjunction with phosphate and carbonate of soda with cinnamon water as a vehicle in gout. Dr Garrod says, "I can confidently affirm that I have already obtained great advantage in the treatment of these diseases (gout and gravel) from the employment of the benzoates<sup>1</sup>." In a healthy individual the administration of benzoic acid does not as has been shewn by Cook<sup>2</sup> stop the formation of the normal amount of uric acid but it masks its presence in the urine and interferes with the Murexide test. That the uric acid was undiminished was also stated formerly by Garrod<sup>3</sup>. But in an abnormal state of things, when there is an excessive amount of glycocine passing unchanged into the blood, the benzoic acid seizes

<sup>1</sup> *Lancet*, April, 1883, p. 673.

<sup>2</sup> *Brit. Med. Journal*, July 7, 1883, p. 9.

<sup>3</sup> *Lancet*, Nov. 1844, p. 240.

upon this and converts it into hippuric acid, and so if glycocine be necessary for the formation of uric acid the amount of the latter must be correspondingly lessened. The remedy however must be given in sufficiently large doses, doses large enough to absorb all the glycocine, and then it may not only prevent the further formation of uric acid, but, as Cook's experiments shew, it may render the uric acid already existing in the blood more soluble and therefore more readily eliminated by the kidneys. To what extent benzoic acid or the benzoates can be given in gout complicated with contracted granular kidney and albuminuria, I am at present unable to say. If albuminuria be not a contra-indication for its administration, this gives it an advantage over the next remedy to which I will refer, viz. salicylic acid, which unfortunately when renal disease exists, not infrequently seems to increase the amount of albumen in the urine. If the urine is free from albumen salicylic acid I think acts better than benzoic acid. Like the latter it combines with glycocine and is eliminated as salicyluric acid; but the true acid must be given made from the oil of wintergreen, not the artificial one made from carbolic acid; and a sufficient quantity must be given, as much as can be borne without head symptoms.

In rheumatic fever I administer 20 grains every hour until the patient complains of slight buzzing in his ears, and I then know that it is producing its physiological action. From 80 to 100 grains are sufficient generally for this. These doses repeated for two or three days cut short the disease, and then from 45 to 60 grains daily, with milk diet for a fortnight, cure most of the cases. In chronic gout however I find that not more daily than from 30 to 45 grains can be generally given. It may be given made into a pill mixed with a little glycerine and powdered gum arabic, 10 grains may be made into three pills, and administered three times a day, and more may be given if the patient can bear it. Or it may be given with rather more than twice the quantity of phosphate of soda, which not only dissolves the salicylic acid, but is also a solvent of uric acid. The remedy answers best when the diet consists simply of milk and farinaceous food and without much meat or beef-tea.

With regard to the administration of the alkaline carbonates which are unquestionably of service in the treatment of gout I can say little which will explain their action. It may be as follows:—Uric acid in an alkaline solution is oxidised into

oxonic acid  $C_4H_5N_3O_4$ , and this may be further decomposed into oxaluric acid, and finally into oxalic acid and urea. Dr Basham pointed out<sup>1</sup> that when under the administration of potash salts the uric acid diminished, oxalates appeared in the urine.

From these considerations it would appear that though by the administration of alkalis the uric acid is destroyed, its place is taken by oxalic acid, and so long as the glycocine passes unchanged into the blood oxalic acid will be produced by the action, in the manner I have already indicated, of the alkalis upon this substance itself, so that measures must be adopted to promote the normal metabolism of that substance.

Another remedy which is used with great advantage in chronic gout is iodide of potassium. As not only uric acid but its derivatives allantoin and hydantoic acid yield glycocine when treated with hydriodic acid, we can easily believe that the presence of an iodide in the blood would prevent the conjugation of glycocine with other substances; but it seems to have a solvent action on the uric acid itself in the blood. Dr Garrod states that it is useful in removing the recent thickening in the tissues

<sup>1</sup> *Practitioner*, Vol. v. 1870.

round joints. And Sir Spencer Wells<sup>1</sup> says he has used it with friction about the joints with most encouraging results. Its action in gouty asthma too is often most beneficial. It probably acts then both as a solvent and as a preventive of the formation of uric acid, but leaves the glycocine still in the blood. It may be urged that hydriodic acid effects the decomposition of uric acid only at a temperature, out of the body, of 160° C., and therefore cannot in the body at the normal temperature of 37°—38° C. produce this result. The fact that the conjugation of benzoic acid and glycocine takes place in the body at the normal temperature, to effect which out of the body requires exactly the same temperature of 160° C., is a complete answer to such an argument. The tolerance for this remedy by gouty persons is very variable—very small doses easily affecting some. Combining it with small doses of tincture of belladonna and giving it two hours after meals I administer as large a dose, 10 or 15 grains, as the patient will bear.

Chloride of ammonium acts most beneficially in some gouty disorders, especially in gouty neuralgia. Now hydrochloric acid decomposes uric acid in the

<sup>1</sup> Wells *On Gout*, 1854, p. 248.



same way as hydriodic acid does, and the action of the chlorides may therefore be explained in the same way.

Dr Symonds<sup>1</sup> recommends common salt in that variety of megrim known as "bilious headache," probably the gouty variety. He says "long periods of exemption from returns of their headaches have occurred to patients who have faithfully observed my directions that they should drink a tumbler of common salt and water every morning an hour before breakfast." Many of the mineral waters which have a reputation for the cure of gout contain, in addition to their laxative elements, a certain amount of the chlorides, and it is probably to the presence of these salts that some portion of the remedial action of the water may be due.

I entertain no doubt as to the service colchicum can render, especially in acute gout—but regret that I can offer no explanation of its action.

As tonics in the intervals between the paroxysms, gentian by improving the digestive function, nux vomica and arsenic by improving the tone of the nervous system, are those which, in my opinion, are most to be relied upon.

<sup>1</sup> "Gulstonian Lectures." *Medical Times*, 1858, p. 495.



